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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR NO. 0050964

July 24, 2002

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

MEMORANDUM

SUBJECT: ***GLUFOSINATE AMMONIUM*** - Report of the FQPA Safety Factor Committee.

NOTE: THIS REPORT REPLACES THE PREVIOUS REPORT OF THE FQPA SAFETY FACTOR COMMITTEE DATED MAY 17, 1999 (HED DOC. NO. 013373).

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Tom Bloem, Risk Assessor
Registration Action Branch 1
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PC Code: 128850

The Health Effects Division (HED) FQPA Safety Factor Committee (SFC) met on July 08, 2002 to evaluate the hazard and exposure data for Glufosinate ammonium with regard to making a decision on the additional safety factor for the protection of infants and children. The SFC determined that reliable data demonstrate that the safety of infants and children will be protected by use of an additional traditional uncertainty factor of 3X. This report replaces the previous report of the FQPA Safety Factor Committee dated May 17, 1999 (HED Doc. No. 013373).

I. HAZARD ASSESSMENT

(*Correspondence:* T. Bloem to B. Tarplee dated June 27, 2002; responses prepared by PV Shah)

1. Adequacy of the Toxicology Database

The following acceptable studies conducted with Glufosinate ammonium were considered by the HIARC:

Acute Neurotoxicity Study in Rats
Two Subchronic Neurotoxicity Studies in Rats
Developmental Toxicity Study in Rats
Developmental Toxicity Study in Rabbits
2- Generation Reproduction Study in Rats

In addition, the following acceptable studies conducted with the L-isomer and metabolites were considered by the HIARC:

Acute Oral Neurotoxicity in Rats with N-Acetyl-L-Glufosinatedisodium
Subchronic Neurotoxicity Study in Rats with N-Acetyl-L-Glufosinatedisodium
Developmental Toxicity Study in Rats with HOE 099730
Developmental Toxicity Study in Rats with HOE 061517
Developmental Toxicity Study in Rabbits with HOE 058192 (L- Isomer)
Developmental Toxicity Study in Rabbits with HOE 099730
Developmental Toxicity Study in Rabbits with HOE 061517

The toxicology database for Glufosinate ammonium is not considered to be complete. The HIARC identified the following data gaps: acute neurotoxicity study conducted in the rat which includes glutamine synthetase (GS) activity measurement in the liver, kidneys, and brain; a developmental neurotoxicity (DNT) study conducted in the rat which includes comparative glutamine synthetase activity measurement in the liver, kidneys, and brain of the pups and mothers. The HIARC also requested additional data to confirm that liver and kidney changes - observed in the absence of histopathological changes - are an adaptive response and not an adverse effect. Kidney and liver function assays should be performed in addition to glutamine synthetase activity measurements. The HIARC concluded that a new subchronic neurotoxicity study in rats **is not** required since it is not expected to provide additional information for regulatory purposes (the doses selected for risk assessment are lower than those that will be tested in a new study).

HIARC applied an additional traditional database uncertainty factor of 3X for the lack of the DNT study with comparative GS measurements. This is consistent with past practice for chemicals requiring a DNT and comparative cholinesterase measurements.

2. Determination of Susceptibility

The HIARC concluded that the available toxicity data for Glufosinate ammonium indicate that the metabolites elicit similar types of effects but at higher doses than the parent compound (i.e., are considered to be less toxic). The single developmental toxicity study conducted with the L-isomer also demonstrates similar effects but at lower doses than Glufosinate ammonium. However, the L-isomer is not the registered active

ingredient. Therefore, the FQPA assessment performed by the HIARC is based on the results of studies conducted with the Glufosinate ammonium.

There is no qualitative or quantitative evidence of increased susceptibility in the developmental toxicity study conducted in rats. Qualitative evidence of increased susceptibility is demonstrated in the rabbit developmental toxicity study since fetal deaths were observed in the presence of lesser maternal toxicity at the same dose. There is also quantitative evidence of increased susceptibility in the rat 2-generation reproduction study. In this study, a decrease in the number of viable pups was observed in the absence of parental toxicity at any dose.

3. Degree of Concern and Residual Uncertainties

Since there is qualitative evidence of increased susceptibility of the young following exposure to Glufosinate ammonium, HIARC performed a Degree of Concern Analysis to: 1) determine the level of concern for the effects observed when considered in the context of all available toxicity data; and 2) identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. If residual uncertainties are identified, HIARC examines whether these residual uncertainties can be addressed by a special FQPA safety factor and, if so, the size of the factor needed. The results of the HIARC Degree of Concern analysis for Glufosinate ammonium follow.

In the rabbit developmental toxicity study, qualitative susceptibility was evidenced at the highest dose tested as a decrease in mean fetal body weight and an increase in the number of dead fetuses/litter in the presence of maternal toxicity (decreased body weight, body weight gain, and food consumption). Considering the overall toxicity profile and the doses and endpoints selected for risk assessment for Glufosinate ammonium, the HIARC characterized the degree of concern for the effects observed in this study as low, noting that the fetal effects of concern occurred only at the highest dose tested and that a clear NOAEL for the effects was established. No residual uncertainties were identified. The NOAEL of 6.3 mg/kg/day identified in this study is used to establish the acute Reference Dose (aRfD) for the Females 13-50 population subgroup.

In the 2-generation reproduction study, quantitative susceptibility was evidenced as reduction in the mean number of viable pups/litter in all generations (with the exception of the F_{2a} generation where the reduction was not statistically significant) in the absence of parental toxicity at any dose level (the HIARC considered the significant increases in kidney weights seen at the mid and high dose in both sexes and both generations to be an adaptive response and not an adverse effect). Considering the overall toxicity profile and the doses and endpoints selected for risk assessment for Glufosinate ammonium, the HIARC characterized the degree of concern for the effects observed in this study as low, noting that clear NOAELs and LOAELs are identified for the offspring effects of concern and the dose-response well-characterized. No residual uncertainties were identified. The extrapolated NOAEL of 2.0 mg/kg/day used to establish the chronic Reference Dose

(cRfD) for all populations is protective of the effects seen in the young in the reproduction study (offspring LOAEL of 18 mg/kg/day is nearly 10-fold higher).

II. EXPOSURE ASSESSMENT

1. Dietary (Food) Exposure Considerations
(*Correspondence:* T. Bloem to B. Tarplee dated June 27, 2002)

Glufosinate ammonium is currently registered for use on a variety of foods including fruits, vegetables, and grains. Glufosinate ammonium is now proposed for use on rice and blueberries. Tolerances are currently established in 40 CFR 180.473 for the combined residues of Glufosinate ammonium and two metabolites (HOE 099730 and HOE 061517) in/on plant and livestock commodities at levels ranging from 0.20-5.0 ppm. There are Codex MRLs established for Glufosinate ammonium in/on various fruit, vegetable, and field crops at levels ranging from 0.05-5.0 ppm.

The available residue database for Glufosinate ammonium consists of field trial data. There are currently no monitoring data available. The field trial data indicate that residues in orchard crops are generally near the LOQ while residue in/on potatoes and the transgenic crops were generally quantifiable. Percent crop treated (%CT) information has also been provided to HED by BEAD based on 1999-2001 data (annual average of <1-5%).

The Dietary Exposure Evaluation Model (DEEM) is used to assess the risk from dietary exposure to Glufosinate ammonium residues in food. These analyses include anticipated residues calculated from field trial data and the available %CT data. Since BEAD data are not available for the new uses, 100% CT will be assumed for these commodities.

2. Dietary (Drinking Water) Exposure Considerations
(*Memorandum:* J. Ravenscroft to B. Tarplee dated July 1, 2002)

The environmental fate data for Glufosinate ammonium, are adequate to characterize drinking water exposure. These data indicate that the compound is mobile and has the potential to contaminate ground water. Glufosinate-ammonium may contaminate surface water through spray drift during application or by runoff from treated areas after application. The stability of Glufosinate ammonium and its degradation products suggests that soil residues may be available for transport for several weeks after application. The potential to contaminate surface water via dissolution in runoff water is also suggested by the soil/water partitioning coefficients and high water solubility. Glufosinate-ammonium is likely to be persistent once it reaches the surface water due to its photolytic stability. Degradates HOE 061517 and HOE 086486, both more mobile than the parent compound, will also tend to reach surface water by runoff.

Targeted monitoring data are not currently available and therefore, EFED models were used to calculate exposure concentrations:

> FIRST (version 1.0) was used to estimate concentrations that might occur in vulnerable surface drinking water supplies. FIRST is a tier I screening model that allows the estimation of acute and chronic concentration values for pesticides in drinking water based upon a vulnerable index reservoir adjacent to fields treated with the pesticide in question. The apple, grape, and tree nut scenario was modeled because it was the highest labeled rate allowed.
>
> SCIGROW (version 1.0) was used to estimate concentrations of Glufosinate that might occur in ground water by leaching. SCIGROW is a regression model designed to estimate a screening level pesticide concentration at an agricultural site which is highly vulnerable to leaching due to a rapidly permeable soil overlying shallow ground water
>
> The drinking water exposure from Glufosinate use on rice was modeled using the interim rice model. The estimates should be used for both acute and chronic EEC's for both aquatic ecological risk assessments, and for drinking water. The EEC's calculated by this method are screening estimates and as such are expected to exceed the true values found in the environment the vast majority of the time.

Glufosinate-ammonium and 3 metabolites, 3-methylphosphinicopropionic acid (MPP, HOE 061517), 2-methylphosphinicoacetic acid (MPA, HOE 064619), and 2-(acetylamino)-4-(hydroxymethylphosphinico)butanoic acid (NAG, HOE 099730/HOE 086486), are included in the Tier I assessment for drinking water as determined in the Metabolism Assessment Review Committee (MARC) meeting on April 24, 2002.

EFED concluded that population exposure could occur in areas where crops are being treated with this herbicide – especially if spray drift is an issue. Another potential human exposure issue via drinking water could occur in the transgenic rice use of glufosinate. There is also concern for accumulation of plant residues left over from harvest which, upon soil incorporation, are released to the soil environment and quickly reconverted to Glufosinate- resulting in another flush of the herbicide. This concern, however, was accounted for in the conservative models used in the drinking water assessment.

3. Residential Exposure Considerations
(*Correspondence:* T. Bloem to B. Tarplee dated June 27, 2002; responses prepared by T. Swackhammer)

Glufosinate ammonium is the active ingredient in registered residential products formulated as a non-selective post-emergence herbicide for use as spot treatments around trees, shrubs, fences, walks, patios, driveways, sidewalks, in flower beds, around houses,

buildings, wooded lots, storage and recreational areas. These products can also be used for lawn renovation at an application rate of 1.36 lb ai/Acre.

Anticipated residential post-application exposure scenarios for children and toddlers include dermal and incidental oral exposure to treated turf following lawn renovations. HED does not routinely assess post-application exposure following spot treatments.

Since no chemical-specific turf residue data has been submitted by the registrant, the standard default assumptions for estimating post-application residues on treated turf as described in the *Standard Operating Procedures (SOPs) For Residential Exposure Assessments*, Draft, 17-DEC-1997 and ExpoSAC Policy No. 11, 22-FEB-2001: *Recommended Revisions to the SOPs for Residential Exposure* are used in the residential exposure assessment.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. FQPA Safety Factor Recommendations

The FQPA SFC recommends that OPP depart from the default 10X additional safety factor and instead use a different additional safety factor of 3X. This recommendation is based on reliable data supporting the findings set forth below.

A. Traditional Additional Uncertainty Factors (Addressing Data Deficiencies)

The FQPA Safety Factor Committee concurs with the HIARC conclusion that a 3X additional traditional database uncertainty factor is required to address data deficiencies in the toxicology database of Glufosinate ammonium (Refer to § I.1.).

B. Special FQPA Safety Factors

Taking into account the HIARC's recommendation regarding the data deficiencies, the FQPA SFC recommends that no Special FQPA Safety Factor is necessary to protect the safety of infants and children in assessing Glufosinate ammonium exposure and risks.

2. Rationale and Findings Regarding Recommendation on Special FQPA Safety Factor

The Committee concluded that no Special FQPA safety factor was needed because:

The toxicology database for Glufosinate ammonium contains acceptable guideline developmental and reproduction studies as well as acute and subchronic neurotoxicity studies. HIARC concluded that there is no quantitative or qualitative evidence of increased susceptibility following *in utero* exposure in the prenatal developmental study in rats. Although there is qualitative evidence of increased susceptibility in the prenatal

developmental study in rabbits and quantitative evidence of increased susceptibility in the 2-generation reproduction study in rats, the HIARC did not identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of Glufosinate ammonium (See §I.3.). The RfDs established are protective of pre-pre/postnatal toxicity following acute and chronic exposures.

There are no residual uncertainties identified in the exposure databases. The dietary food exposure assessment includes anticipated residues calculated from field trial data and available percent crop treated information from BEAD (100% crop treated is assumed for the new uses). Dietary drinking water exposure is based on conservative modeling estimates and the Residential SOPs will be used to assess post-application exposure to children as well as incidental oral exposure of toddlers. These assessments will not underestimate the exposure and risks posed by Glufosinate ammonium.

3. Application of the FQPA Safety Factors (Population Subgroups / Risk Assessment Scenarios)

The FQPA safety factor recommendation is for a 3X traditional database uncertainty factor to address data deficiencies and no additional Special FQPA safety factor. The 3X safety factor should be applied to all dietary and non-dietary residential exposure scenarios. No other FQPA safety factor would be appropriate for Glufosinate ammonium.

4. Summary of FQPA Safety Factors

Summary of FQPA Safety Factors for Glufosinate ammonium				
	LOAEL to NOAEL (UF_L)	**Subchronic to Chronic (UF_S)**	**Incomplete Database (UF_{DB})**	**Special FQPA Safety Factor (Hazard and Exposure)**
Magnitude of Factor	1X	1X	**3X**	1X
Rationale for the Factor	No LOAEL to NOAEL extrapolations performed	No subchronic to Chronic extrapolations performed	**For lack of developmental neurotoxicity study with comparative glutamine synthetase measures**	No residual uncertainties regarding pre- or post-natal toxicity or completeness of the toxicity or exposure databases.
Endpoints to which the Factor is Applied	Not Applicable	Not Applicable	**All dietary and non-dietary residential exposure assessments**	Not Applicable

Jess Rowland
07/23/02 02:00 PM

To: Brenda Tarplee/DC/USEPA/US@EPA
cc:
Subject: for whatever this is worth!!

7. Recommendation for a Developmental Neurotoxicity Study

The HIARC concluded that there is a concern for developmental neurotoxicity resulting from exposure to bifenthrin. The study is required based on evidence of neurotoxicity observed in the developmental toxicity, 2-generation reproduction, acute and subchronic neurotoxicity, subchronic and chronic oral toxicity, and dermal toxicity studies.

The HIARC concluded that a Database Uncertainty Factor (UFDB) of 3x is required for the lack of a DNT study because the available data indicate that the results of the DNT study might impact the doses selected for risk assessment. This is based on the assumption that doses in the DNT would be similar to those examined in the 2-generation rat reproduction study where no toxicity to the offsprings was observed; the NOAEL was > 5.0 mg/kg/day (HDT). This NOAEL is approximately 5X higher than the NOAEL of 1.3 mg/kg/day used for establishing the chronic RfD and therefore the chronic RfD would address the concerns for offspring toxicity in the DNT. However, the NOAEL of 32.8 mg/kg used for establishing the acute RfD is higher than the NOAEL for offspring toxicity and therefore the acute RfD would not address the toxic effects in pups following a single exposure.

A 3X UF was viewed to be adequate (as opposed to a 10x) the available DNT data demonstrate that a 3-fold UF is generally sufficient to address the uncertainty that results from a missing DNT study (A retrospective analysis of twelve developmental neurotoxicity studies submitted to OPPTS, Presented to the SAP, December 8-9, 1998).

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FQPA SAFETY FACTOR COMMITTEE MEETING

July 8, 2002

GLUFOSINATE AMMONIUM

Name	Division/Branch
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Tina Levine	BEAD
John Ravenscroft	EFED
Kathy Monk	SRRD
Jeffrey Herndon	HED / RAB1
Beth Doyle	HED
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Tom Bloem	HED/RAB1
Dennis Edwards	AD
Susan Makris	HED/TOX
Jose Rowel	HED/SIMB.
Ed Rodia	HED
Margaret Stasikowski	HED
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Chemical:	**Butanoic acid, 2-amino-4-(hydroxy-methyl**
PC Code:	**128850**
HED File Code	**21500 FQPA**
Memo Date:	***07/24/2002***
File ID:	**TX050964**
Accession Number:	**412-03-0016**

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